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Brief Reviews

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Interfering with Immunity: Detrimental Role of Type I IFNs during Infection

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Type I IFNs are known to inhibit viral replication and mediate protection against viral infection. However, recent studies revealed that these cytokines play a broader and more fundamental role in host responses to infections beyond their well-established antiviral function. Type I IFN induction, often associated with microbial evasion mechanisms unique to virulent microorganisms, is now shown to increase host susceptibility to a diverse range of pathogens, including some viruses. This article presents an overview of the role of type I IFNs in infections with bacterial, fungal, parasitic, and viral pathogens and discusses the key mechanisms mediating the regulatory function of type I IFNs in pathogen clearance and tissue inflammation. ***The Journal of Immunology*****, 2015, 194: 2455–2465.**

Interferons are a family of cytokines first identified in the 1950s on the basis of their antiviral function (1). Since their discovery, IFNs have been divided into three types based on their respective cell surface receptors. The type I IFNs are by far the largest family and consist of >20 individual members, such as IFN-α, -β, -ε, -κ, and -δ (2). These cytokines bind to cell surface IFN-α receptor (IFNAR) that is composed of two subunits: IFNAR1 and IFNAR2 (3, 4). Type I IFNs are produced in large quantities following viral infection and are regarded as the archetypal antiviral cytokine. The essential host-protective role for type I IFNs in controlling viral infection is exemplified by the observation that type I IFNR-deficient (*Ifnar1*$^{-/-}$) mice quickly succumb to a variety of viral infections compared with wild-type (WT) mice (4–8).

The sole type II IFN, IFN-γ, signals through the IFN-γ receptor (IFNGR) complex comprising IFNGR1 and IFNGR2 subunits (9). IFN-γ is produced predominantly by activated T and NK cells and plays a major role in activating immune cells during infection with intracellular pathogens (reviewed in Ref. 9). Deficiency in IFN-γ production or signaling leads to loss of resistance to *Mycobacteria* (10), *Listeria* (11), and *Leishmania* (12). Furthermore, hereditary loss-of-function mutations in the IFN-γ or IL-12 signaling pathways in humans, known as Mendelian susceptibility to mycobacterial diseases, results in increased susceptibility to infection with mycobacteria (13–16), establishing the critical function for the IFN-γ/IL-12 axis in immunity to intracellular infection.

The more recently identified type III IFNs include IFN-λ1, IFN-λ2, and IFN-λ3. The receptor for type III IFNs contains two subunits, the unique IFN-λ receptor (IFNLR1) and the shared IL-10R2 subunit that is involved in IL-10, IL-22, and IL-26 signaling (17, 18). Interestingly, despite using different cell surface receptors, type III IFNs exhibit similar biological activities to type I IFNs because both types of IFNs activate the same intracellular signaling pathways (reviewed in Ref. 19). However, the magnitude of STAT activation and subsequent biological activities induced by type I IFNs are often greater than those induced by type III IFNs (19). In addition, unlike the type I IFNR, which is expressed almost ubiquitously on all cells, IFNLR1 is expressed predominantly on epithelial cells (20). Therefore, the biological role of type III IFNs is believed to be much more restricted than that of type I IFNs.

It is perceived that type I and type III IFNs are quintessential mediators of antiviral immunity, and IFN-γ is required for resistance to intracellular bacterial and parasitic infections. However, although originally discovered based on their antimicrobial activities, type I IFNs are now known to exhibit other functions, such as antiproliferative and immunoregulatory properties (reviewed in Ref. 21). Some of the classically described immunoregulatory activities are the ability to upregulate MHC class I expression, promote NK cell cytotoxicity, and affect maturation and recruitment of myeloid cell populations (reviewed in Ref. 22). Importantly, recent studies demonstrated that type I IFNs can play a negative role in the control of a diverse range of pathogens. This review summarizes the biological effects of type I IFNs on host resistance to infections, with a focus on the mechanisms underlying the

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Abbreviations used in this article: cGAS, cyclic GMP–AMP; Ch25h, cholesterol 25-hydroxylase; IAV, influenza A virus; IFI16, IFN-γ–inducible protein 16; IFNAR, IFN-α receptor; IFNGR, IFN-γ receptor; IRF, IFN regulatory factor; IRG, IFN-regulated gene; LCMV, lymphocytic choriomeningitis virus; LLO, listeriolysin O; LRV, *Leishmania* RNA virus; 2′5′OAS, 2′5′-oligoadenylate synthase; PKR, protein kinase R; poly I:C, polyinosinic-polycytidylic acid; PRR, pattern recognition receptor; RIG, retinoic acid–inducible gene; SOCS1, suppressor of cytokine signaling 1; STING, stimulator of IFN gene; TB, tuberculosis; TBK1, tank-binding kinase 1; WT, wild-type.

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induction and detrimental function of the cytokines in infection.

Type I IFN induction by pathogens

Induction of type I IFNs has been studied extensively over the last two decades, initially in viral infections and more recently in intracellular bacterial infections. Three distinct pathways were shown to be critical in the induction of these cytokines. TLRs (reviewed in Ref. 23), the retinoic acid–inducible gene (RIG)-like helicases (reviewed in Ref. 24), and the more recently discovered cytoplasmic DNA sensors (25–29).

The TLRs are membrane-bound pathogen recognition receptors (PRRs) expressed either on the cell surface (TLR1, 2, 4, 5, and 10) or in endosomes (TLR3, 7, 8, and 9) (23). TLR2, 3, 4, 7, 8, and 9 were shown to induce type I IFNs via recognition of their respective pathogen-associated molecular pattern ligands (30). With the exception of TLR3 and TLR4, MyD88 is the adaptor molecule that mediates type I IFN production for all TLRs. TLR3 and TLR4 induce IFN-β production via the adaptor molecule TRIF (23). Activation of either the MyD88-dependent or -independent pathway leads to activation of members of the IFN regulatory factor (IRF) family, most notably IRF3 and IRF7 (31). IRF3 and IRF7 bind to the promoters of type I IFN genes and initiate their transcription.

The RIG-I like family of helicases contains the members RIG-I and melanoma differentiation-associated protein 5, which recognize cytoplasmic RNA and interact with the mitochondrial membrane-bound IFN-β promoter stimulator 1 (24). This, in turn, interacts with tank-binding kinase 1 (TBK1) to activate IRF3 and IRF7, leading to transcription of IFN genes.

In addition, cytoplasmic DNA sensors, such as IFN-γ–inducible protein 16 (IFI16) (27), DNA-dependent activator of IRFs (26), and cyclic GMP–AMP synthase (cGAS) (25, 28), can bind dsDNA and trigger endoplasmic reticulum–associated adaptor molecule stimulator of IFN genes (STING) (32), TBK1, and IRF3-dependent type I IFN induction (31).

Type I IFN signaling pathway

The IFN signaling cascade is initiated by the binding of the cytokines to the high-affinity receptor subunit IFNAR2, followed by binding of the binary complex to IFNAR1 (reviewed in Refs. 3, 33). This receptor engagement induces phosphorylation of the intracellular receptor-associated JAK kinases JAK1 and TYK2, which leads to phosphorylation, dimerization, and nuclear translocation of STAT transcription factors. In addition to inducing STAT homo- and heterodimers (34), type I IFNR engagement results in the formation of the well-studied signaling molecule IFN-stimulated gene factor 3, a complex composed of STAT1:STAT2 and IRF9 (35). In addition to STAT1:STAT2, other STAT homodimers and heterodimers can be induced by type I IFNs in some cell types. Activated STATs translocate to the nucleus where they bind to the promoters of IFN-regulated genes (IRGs) to induce their transcription. Differential combinations of STAT homo- and heterodimers are believed to trigger functionally distinct genes, although the mechanisms governing such associations are poorly understood. Finally, other signaling mechanisms, such as PI3K and MAPK pathways, also contribute to the generation of type I IFN signaling (36). The signaling of type I IFNs via different intracellular signaling mechanisms is postulated to be responsible for cell-type specific functions of IFNs (reviewed in Ref. 37).

Hundreds of IRGs have been reported. Bioinformatic approaches have led to the identification of IFN-inducible gene signatures (38–40), although the precise function of individual IRGs in an immune response is still being elucidated (39). This IFN gene signature is traditionally referred to as the "antiviral state" (41) and forms the basis by which type I IFNs confer their antiviral effector functions. Among the most characterized IRGs are antiviral proteins, such as Mx proteins, protein kinase R (PKR), and 2′5′-oligoadenylate synthase (2′5′OAS) (reviewed in Ref. 42), which suppress viral replication by binding to viral polymerases and ribonucleoproteins (as in the case of Mx) (43), inhibiting gene translation (PKR) (44), or cleaving viral ssRNA (2′5′OAS) (45).

Regulatory function of type I IFNs in infection

Although the host-protective functions of type I IFNs have been well established in viral infection, their role in the host response to other microorganisms has been recognized only recently (reviewed in Refs. 33, 46–48). As discussed below, type I IFNs are now known to play a pivotal role in regulating the outcome of many infections. This review summarizes their detrimental function in immunity against a group of highly diverse pathogens, with the aim of understanding the cytokines' biological functions in infection. Because the role of type I IFNs in bacterial infections has been comprehensively discussed recently (49), only some bacterial pathogens are discussed below.

Listeria

Listeria monocytogenes is a Gram-positive bacterium known to cause disease when ingested (50), and cell-mediated immunity is essential for host control of the infection. *L. monocytogenes* is initially phagocytosed by macrophages and dendritic cells and then escapes from the phagosome into the cytosol by secreting the listeriolysin O (LLO) toxin (51). Critically, LLO and subsequent bacterial escape into the cytoplasm are required for type I IFN production because LLO-deficient *Listeria* strains do not induce type I IFNs (51). Pathogenicity of LLO is further exemplified by the observation that *Bacillus subtilis* engineered to express LLO also escapes into the cytoplasm and induces IFN-β production and a subsequent IFN-dependent gene signature (51).

Once in the cytosol, *L. monocytogenes* produce cyclic diadenosine monophosphate that induces type I IFN in an IRF3-dependent, MyD88-independent manner (52–54). Interestingly, a recent study demonstrated that, in human cells, *Listeria*-derived DNA, rather than cyclic diadenosine monophosphate, triggers IFN-β production via cytosolic DNA sensors IFI16 and cGAS (55). This occurs, in part, because murine cells are more responsive to bacterial cyclic dinucleotides than human cells (28, 56).

Intravenous or i.p. infection with the bacteria induces type I IFN expression in mice (52, 57), and *Ifnar1*$^{-/-}$ mice are more resistant to infection compared with WT mice (53, 58, 59). In addition, pretreatment of mice with polyinosinic-polycytidylic acid (poly I:C), an inducer of type I IFNs, increases their susceptibility to *L. monocytogenes* infection (53).

Considerable work has been performed to define the mechanisms by which type I IFNs enhance host susceptibility to infection. Type I IFNs were shown to increase lymphocyte apoptosis (53, 59, 60), enhance macrophage cell death (61, 62), antagonize IFN-γ signaling by downregulating the IFNGR on APCs (63), inhibit neutrophil migration (64), and reduce the production of protective IL-12 and TNF-α (58, 59). Together, these findings suggest that the bacterium-induced type I IFNs can modulate multiple protective mechanisms to impair survival of the infected host.

A recent study discovered that type I IFNs suppress the immune system via induction of 25-hydroxycholesterol, an oxysterol that is produced by the IFN-inducible gene cholesterol 25-hydroxylase (Ch25h) (65). Mice deficient in Ch25h exhibit increased inflammasome-dependent IL-1β release, IL-17 production, and neutrophil recruitment. Importantly, *L. monocytogenes*–infected Ch25h-deficient mice display reduced bacterial numbers in spleens and livers compared with WT mice (65), implicating a role for 25-hydroxycholesterol in the type I IFN–dependent suppression of immunity to the infection. Nevertheless, it remains to be determined whether this pathway represents a common mechanism mediating type I IFN–dependent immune suppression.

Mycobacteria

Mycobacteria are slow-growing intracellular bacteria. *Mycobacterium tuberculosis* is the causative organism for tuberculosis (TB) and is responsible for 1.3 million deaths annually (66). Approximately 10% of infected individuals eventually develop active disease. In both humans and mice, host control of *M. tuberculosis* depends on Th1 cell-mediated immunity. IFN-γ is essential for activating macrophages to contain intracellular infection (reviewed in Ref. 67). Although avirulent mycobacteria are effectively eliminated by host immunity, virulent mycobacteria deploy multiple strategies to evade the host antimicrobial machinery, allowing their survival within host macrophages.

Recent evidence suggests that type I IFNs may play a previously unappreciated role in *M. tuberculosis* persistence and TB pathogenesis. In both human and mouse macrophages, type I IFNs are induced following infection with virulent *M. tuberculosis* but not avirulent vaccine strains, such as *M. bovis* BCG (68, 69). Interestingly, the mycobacterial virulence factor ESX-1, which is absent in BCG (70), is required for type I IFN production (68, 69). ESX-1 was shown to permeabilize the phagosomal membrane and thus, allow phagosomal mycobacterial products to access cytoplasmic innate recognition machinery (71, 72). Indeed, mycobacterial extracellular DNA was shown to activate IRF3 to induce IFN-β production in a STING/TBK1-dependent manner (71).

The induction of a large number of IFN-related genes was observed in *M. tuberculosis*–infected mice, as well as *M. bovis*–infected cattle (69, 73–75). In humans, a comparable IFN-inducible gene signature was observed in the blood of TB patients, as well as in 10–25% of latently infected individuals (76). Further analysis revealed that 86 transcripts can distinguish active TB from other types of inflammatory conditions, such as systemic lupus erythematosus (76), which is known to be associated with an enhanced type I IFN gene signature. This finding suggests that the whole-blood IFN signature could be useful in identifying active TB disease. However, recent studies reported that a similar set of IFN-inducible genes can be detected in other inflammatory diseases, such as melioidosis (77) and sarcoidosis (78), arguing that the clinical potential for the IFN-inducible gene signature in TB diagnosis needs to be evaluated more carefully.

Because avirulent mycobacteria do not induce type I IFNs, it is hypothesized that type I IFN production is associated with mycobacterial virulence and increased host susceptibility. Indeed, infection of mice with hypervirulent clinical isolates results in higher type I IFN production compared with less virulent laboratory strains, and the increased type I IFN levels are associated with reduced expression of Th1 cytokines TNF-α and IL-12 (79–81). Importantly, *Ifnar1*$^{-/-}$ mice and *Irf3*$^{-/-}$ mice (unable to induce IFN-β) demonstrate lower bacterial burden compared with WT animals (71, 79, 81). Furthermore, intranasal treatment of mice with the type I IFN inducer poly I:C exacerbated pulmonary TB in WT, but not *Ifnar1*$^{-/-}$, mice (82).

Although the exact mechanisms by which type I IFNs exacerbate TB infection are currently being investigated, recent works revealed a number of modes of action. For instance, exogenous or *M. tuberculosis*–induced type I IFNs were shown to suppress expression of the *IL1B* gene in human macrophages (68). A separate study found that blockade of IFN-β–induced IL-10 signaling partially restored *IL1B* expression, indicating that type I IFNs may act indirectly to confer their negative effects via IL-10 (83). Because IL-10 has been known to exacerbate murine mycobacterial infections under some circumstances (84), IL-10 induction by type I IFNs could be one mechanism by which type I IFNs impair resistance to mycobacterial infection (85–87). Interestingly, a recent study suggests that *M. tuberculosis*–induced type I IFN production can be regulated by IL-1β through PGE_2 (88). PGE_2 administration suppresses type I IFN production and increases survival in treated mice, suggesting a cross-regulation between the IL-1β and type I IFN pathways and that antagonism of type I IFN production via PGE_2 could be used as a potential therapy for active TB.

In addition, type I IFNs can suppress IFN-γ signaling by downregulating IFNGR1 expression (63, 82, 89), suggesting that their detrimental effect directly involves the antagonism of type II IFN signaling. Interestingly, Desvignes et al. (90) found that, in the absence of IFN-γ signaling, type I IFNs play a host-protective role during *M. tuberculosis* infection, because mice deficient in both type I and type II IFNR components have worse pathology and increased mortality compared with single type II IFNR–deficient animals. This finding suggests that type I IFNs are detrimental only when IFN-γ–dependent immune mechanisms are activated. In line with this work, *M. tuberculosis* strains known to trigger high levels of type I IFN also induce increased levels of the negative regulator of IFN signaling, suppressor of cytokine signaling 1 (SOCS1) (81). Moreover, *Ifnar1*$^{-/-}$ mouse macrophages express lower levels of *Socs1* during mycobacterial infection, and IFN-γ–activated *Socs1*$^{-/-}$ macrophages have lower intracellular bacteria as a result of the increased IFN-γ signaling (91). These experimental findings, together with the clinical observation that increased SOCS protein expression correlates with increased disease severity (92, 93), hint that a detrimental role for type I IFNs in *M. tuberculosis* infection is to antagonize host-protective functions of IFN-γ.

TB is not the only mycobacterial disease associated with type I IFN induction. Self-healing tuberculoid leprosy is traditionally associated with the development of a Th1 response, whereas disseminated lepromatous leprosy is characterized by a Th2 response. Interestingly, this historical view was revised recently by placing type I IFN as a central regulator determining the outcome of *M. leprae* infection. Lepromatous leprosy is associated with the development of an IFN-β–inducible gene signature in the blood (94). Importantly, type I IFNs are shown to increase bacterial burden and tissue pathology by limiting IFN-γ–dependent antimicrobial activity through production of the immunosuppressive cytokine IL-10 (94).

Franciscella

Franciscella tularensis is the causative bacterium for the highly lethal disease tularemia (reviewed in Ref. 95). Although human disease is shown to occur via zoonotic transmission from arthropods or other infected animals, *F. tularensis* has gained increasing attention because of its potential use in bioterrorism (96). Host control of *F. tularensis* infection is dependent on cell-mediated immunity (reviewed in Refs. 97, 98). *F. tularensis* infects macrophages, neutrophils, and dendritic cells and establishes a replicative niche in macrophages by inhibiting acidification of the phagosome and escaping into the cytoplasm (99–101). Interestingly, induction of IFN-β during *F. tularensis* infection is dependent on access of the bacterium to the cytoplasm (102). This cytokine induction appears to be IRF3 dependent but TLR independent (102, 103). Although the PRR responsible for type I IFN induction during *F. tularensis* infection remains to be identified, IFN-β expression is greatly reduced in STING-deficient cells (104), suggesting a possible involvement of DNA-sensing receptors, such as cGAS and IFI16, in the process (105). Furthermore, cytosolic bacterial nucleic acids from *F. tularensis* (103) were shown to induce absent in melanoma 2 inflammasome complex formation and secretion of the proinflammatory cytokines IL-1β and IL-18 (102, 104, 106, 107), providing further evidence that bacterial DNA is able to access cytoplasmic PRRs.

The role of type I IFNs in *F. tularensis* infection is poorly understood. Although type I IFN production is critical for activation of the host-protective absent in melanoma 2 inflammasome during *F. tularensis* infection (102–104), type I IFNR–deficient mice were shown to be more resistant to intradermal infection than WT animals (108). This latter study suggests that type I IFNs can negatively regulate the accumulation of IL-17–producing cells, thereby impairing neutrophil accumulation and resistance to *F. tularensis* infection (108, 109). However, other mechanisms may exist. As reviewed by Furuya et al. (109), neutrophil recruitment following pulmonary *F. tularensis* infection is independent of IL-17, suggesting that the mechanism of action of type I IFNs operating in intradermal infection (108) is different from that in intranasal infection (110).

Salmonella

Salmonella are Gram-negative bacteria. *Salmonella enterica* serovar Typhi (*S. typhi*) and *S. paratyphi* are causative organisms for the disease typhoid fever. Host control of infection is dependent on macrophages and neutrophils, as well as the production of IL-6, IL-1β, IL-18, IFN-γ, and TNF-α (reviewed in Ref. 111). Because *S. typhi* is an exclusively human pathogen, studies in mice use the nontyphoidal *S. enterica* serovar Typhimurium (*S. typhimurium*) strain. Although *Salmonella*-derived LPS is known to induce IFN-β production in macrophages in a TLR4/TRIF-dependent manner (112), a more recent study demonstrated that *S. typhimurium* RNA also triggers IFN-β production in fibroblasts via a RIG-I/MAVS–dependent pathway (113).

A role for type I IFN in *Salmonella* infection in vivo was recognized only recently. Following i.v. infection with *S. typhimurium*, *Ifnar1*$^{-/-}$ mice show reduced mortality associated with increased macrophage numbers compared with WT mice (114). Type I IFNs are responsible for the *S. typhimurium*–induced cell loss by triggering RIP1- and RIP3-dependent necroptosis, an inflammatory form of cell death. Interestingly, type I IFNs also can promote necroptosis in mice administered LPS and TNF-α (115), suggesting that this mechanism could play a role in other infection and/or inflammation settings in which the host response is mediated by macrophages.

Chlamydia

Chlamydia trachomatis is an intracellular bacterium and the causative organism of the sexually transmitted infection Chlamydia that is responsible for reproductive morbidity in females. Host control of *Chlamydia* infection is predominantly dependent on IFN-γ, although other unidentified mechanisms have been investigated (reviewed in Ref. 116).

The role of type I IFNs in *Chlamydia* infection is not as well defined as in other intracellular bacterial-infection models. *C. trachomatis* and the murine pathogen *C. muridarum* infect and replicate in epithelial cells and were found to induce IFN-β in a TLR3/TRIF- (117, 118) or cGAS/STING-dependent manner (119–121). *Ifnar1*-deficient mice exhibit reduced bacterial burden compared with WT mice following genital (122) and respiratory (123) infection with *C. muridarum*, revealing a detrimental role for type I IFNs in regulating mucosal immunity to this intracellular pathogen. However, type I IFNs do not appear to interfere with the development of a Th1 response to *C. trachomatis* because IL-12, TNF-α, and IFN-γ expression were unaffected in both studies (122, 123). Instead, the increased resistance of *Ifnar1*$^{-/-}$ mice was found to be associated with reduced macrophage apoptosis, suggesting that type I IFNs impair host immunity by inducing the death of host-protective effector cells.

Interestingly, in contrast to these studies, mice deficient in the mucosal tissue–specific IFN-ε demonstrate increased bacillary burden and disease symptoms compared with WT mice (124). Although the IFN-ε–protective mechanisms are still under investigation, it appears that different members of the type I IFN family may have distinct functions in this infection model.

Staphylococcus

Staphylococcus aureus is a Gram-positive bacterium and is responsible for significant morbidity and mortality in infection with antibiotic-resistant strains (125). Innate myeloid cells, such as neutrophils and macrophages, play an essential role in the clearance of *S. aureus* (126, 127). This extracellular bacterium was unexpectedly shown to induce type I IFN production. At least three distinct innate-sensing mechanisms

have been proposed: (1) the short sequence-repeat region of *S. aureus* surfactant protein A triggers IFN-β production in human and mouse airway epithelial cells in vitro (128); although the molecular pathway has yet to be defined, the observation that the cytokine induction requires internalization of surfactant protein A hints at a possible involvement of an intracellular recognition mechanism in the process; (2) *S. aureus* DNA activates mouse dendritic cells to produce IFN-β in a TLR9-dependent manner (129); and (3) microbial products, such as peptidoglycan, released during bacterial autolysis can activate the NOD2/IRF5-dependent pathway to produce IFN-β in mouse dendritic cells (130).

Interestingly, a recent study demonstrated that a hypervirulent strain of *S. aureus* induces a higher level of IFN-β production and causes greater mortality compared with its less virulent counterparts (130), suggesting an association between type I IFN and bacterial virulence. Type I IFNs appear to enhance pathology in *S. aureus* infection by increasing TNF-α and IL-6 production (128–130), as well as neutrophil recruitment (128, 130). Therefore, although neutrophils are essential for the clearance of *S. aureus*, their excessive recruitment causes tissue inflammation, leading to reduced resistance in this setting. Indeed, *Ifnar1*$^{-/-}$ mice are protected against lethal *S. aureus* pneumonia (128). Similarly, *Tlr9*$^{-/-}$ mice, which are unable to produce IFN-β in response to the infection, demonstrate reduced mortality, suggesting that the TLR9 signaling pathway contributes to IFN-β induction and mortality in vivo (129).

In contrast to resistance to intracellular pathogen infection, Th1-dependent cell-mediated immunity plays a lesser role in controlling extracellular bacteria. Therefore, these findings on *S. aureus* infection provide interesting insights into the negative role of type I IFNs in infection and indicate that type I IFNs play a broader role in host susceptibility to infection beyond suppressing IFN-γ–induced antimicrobial effector mechanisms.

Candida

Candida albicans, a fungus residing predominantly on mucosal surfaces, can cause opportunistic infections and presents a significant burden to immunocompromised individuals (reviewed in Ref. 131). Neutrophils and monocytes/macrophages, through the production of NADPH and myeloperoxidase, play a critical role in the host control of the fungal infection (reviewed in Ref. 132).

Induction of IFN-β by *Candida* spp. in dendritic cells was shown to depend on an active phagocytosis process and requires C-type lectin and TLR7 (133). Macrophages stimulated in vitro with poly I:C exhibit reduced phagocytic potential and impaired killing of phagocytosed *C. albicans* (134). Addition of anti–IFN-α/-β– or anti–IFN-β–neutralizing Abs restored the candidacidal activity of macrophages (134). In a mouse model of disseminated candidiasis with *C. glabrata*, deficiency in type I IFN signaling results in enhanced tissue pathogen clearance compared with control animals (133). Similarly, *C. albicans*–infected *Ifnar1*$^{-/-}$ mice show increased survival compared with their WT counterparts that is due to reduced recruitment and activation of inflammatory monocytes and neutrophils (135). In addition, treatment of mice with poly I:C increases *Candida* disease severity in a type I IFN–dependent manner (134, 136, 137). Therefore, these data suggest a model in which type I IFNs regulate the outcome of infection through their regulatory role on monocytes and neutrophils.

Trypanosoma

Trypanosoma are parasites that are usually transmitted by insect vectors. Control of *T. cruzi* infection is critically dependent on IFN-γ produced by activated NK cells and T cells (138). Although the induction of type I IFNs by *T. cruzi* and *T. equiperdum* has been observed for decades (139, 140), only recently has work addressed the significance of the cytokines in the resistance to the parasite. Studies performed using infected murine bone marrow–derived dendritic cells and macrophages indicate that *T. cruzi*–induced IFN-β is predominantly produced in a TRIF-dependent manner (141), although it is not known whether TLR3, TLR4, or both are responsible for type I IFN induction.

Importantly, the level of IFN-β induction in *T. cruzi*–infected mice correlates with disease severity, suggesting an association between type I IFNs and worsened disease outcome (142). Recently, Chessler et al. (143) reported that *Ifnar1*$^{-/-}$ mice show improved survival following lethal *T. cruzi* challenge, which is associated with a reduction in IFN-γ expression in the splenocytes of WT mice compared with *Ifnar1*$^{-/-}$ animals; this suggests that inhibition of IFN-γ production or signaling might be one of the mechanisms by which type I IFNs enhance host susceptibility to the infection (143). Indeed, Lopez et al. (144) found that mice deficient in a negative regulator of type I IFN signaling were unable to control infection because of significantly reduced IFN-γ induction.

Leishmania

Leishmania is a genus of parasites that infect human hosts via sandfly bites and cause leishmaniasis (reviewed in Ref. 145). Resistance to *Leishmania* is dependent on Th1 cell responses, whereas susceptibility to infection is associated with Th2 responses (reviewed in Ref. 146). Although early studies suggested that type I IFNs enhance resistance to *L. major* (147, 148), possibly by promoting the expression of NOS2, IL-12p40, and IFN-γ (147, 149), recent reports showed that type I IFNs are detrimental for control of other *Leishmania* spp.

Type I IFNs were shown to prevent parasite clearance in parasite-infected macrophages and mice. Incubation of *L. amazonensis*– and *L. braziliensis*–infected macrophages with exogenous IFN-β increases parasite burden as a result of reduced superoxide production (150). Moreover, macrophages deficient in the type I IFN–inducible dsRNA-dependent kinase PKR clear *L. amazonensis* more efficiently and exhibit reduced IL-10 production compared with WT macrophages (151). Treatment of infected human macrophages with poly I:C promotes parasite replication in a PKR-dependent manner, although the role of type I IFN was not formally established. In vivo, *L. amazonensis*–infected *Ifnar1*$^{-/-}$ mice show reduced parasite load, as well as decreased pathology, compared with WT mice (152). The increased resistance is associated with enhanced recruitment of neutrophils. In this case, neutrophils are believed to mediate pathogen killing by releasing enzymes, such as elastase and myeloperoxidase (152).

Interestingly, the negative roles of type I IFN in *Leishmania* infection are mainly reported in infections with *L. amazonensis* and *L. braziliensis*, which form the New World species of *Leishmania* that are predominant in the western hemisphere. It is possible that the beneficial or detrimental role of type I IFN in the infection is dependent on the particular species of *Leishmania* present. Interestingly, the frequently metastasizing *L. braziliensis* and *L. guyanensis* contain the dsRNA virus *Leishmania* RNA virus (LRV)1 (153–155). Mice infected with *L. guyanensis* containing this virus produce IFN-β in a TLR3-dependent manner, and $TLR3^{-/-}$ mice display reduced footpad swelling (156). Although an isolate of *L. major* was found to contain LRV2, the effect of the virus on the outcome of *L. major* infection was not investigated (157). It is possible that the detrimental role of type I IFNs in *Leishmania* infection is due to the presence of LRV1 or other *Leishmania* viruses.

Plasmodium

Plasmodium are zoonotic parasites that are able to infect humans and cause malaria (158) and are responsible for ~1 million deaths annually. Host control of the parasite is believed to be dependent on T lymphocytes, the cytokines IFN-γ and TNF-α, and Abs (reviewed in Ref. 159). Multiple innate-sensing pathways were shown to mediate type I IFN induction by the parasite. In addition to TLR7/TLR9-dependent mechanisms (160, 161), type I IFNs can be induced in a STING, TBK1, IRF3/IRF7–dependent manner via AT-rich stem-loop DNA (162). *P. berghei*–derived RNA also can trigger IFN-β production in a melanoma differentiation-associated protein 5/MAVS-dependent manner (163). However, it is unknown how these pathogen products gain access to the cytosol.

Although it is evident that type I IFNs can be produced by malaria parasite–infected cells in vitro, the cytokines' function during infection in vivo is less clear. Type I IFNs were shown to mediate protection against blood-stage (164) and liver-stage (163, 165) malaria in infected animals. However, recent studies revealed that type I IFNs increase host susceptibility to cerebral malaria (162, 166).

Following *P. berghei* ANKA infection, parasitemia and clinical scores are significantly lower in $Ifnar1^{-/-}$ mice compared with WT animals (167). Interestingly, the enhanced resistance is associated with increased numbers of IFN-γ–secreting $CD4^+$ T cells (167). In a follow-up study, type I IFNs were shown to act directly on splenic conventional dendritic cells to impair their ability to phagocytose parasites and prime Th1 cells (168). In addition, deficiency in type I IFN signaling results in an increase in MHC class II expression. Importantly, Ab blockade of type I IFNR prevents disease progression and the death of infected mice. Together, these findings reveal that type I IFNs regulate parasite control by suppressing IFN-γ production and suggest that blockade of type I IFN signaling during severe malaria infection may provide a novel adjunct therapy (168).

Lymphocytic choriomeningitis virus

Lymphocytic choriomeningitis virus (LCMV), a member of the Arenaviridae family, is rodent borne but can be transmitted to humans in rare cases (169). It has been used extensively in laboratory research to study immune responses to viral infection owing to the fact that different isolates of the virus can lead to either acute or persistent infection (170). For example, infection of mice with LCMV Armstrong or Clone 13 leads to acute (171) and persistent (172) infection, respectively. Unlike acute infection, in which viral control is $CD8^+$ T cell dependent (173–175), clearance of persistent infection is dependent on $CD4^+$ T cells and IFN-γ (173, 176, 177).

The requirement for type I IFNs for host survival following acute LCMV infection is well established, because mice deficient in the type I IFNR are susceptible to the viral infection as a result of uncontrollable viral replication (5, 178–180). Although persistent LCMV infection is known to result from functional T cell exhaustion (reviewed in Ref. 181) associated with elevated PD-1 expression on T cells (182), as well as IL-10 and PD-L1 expression in infected mice (183, 184), a role for type I IFNs in this process was poorly understood until recently.

Two recent studies demonstrated that, during chronic infection, the significantly elevated levels of PD-L1 and IL-10, as well as viral loads, are significantly reduced in $Ifnar1^{-/-}$ mice or WT animals treated therapeutically with a blocking Ab to the receptor (176, 177). Thus, it appears that failure to control chronic LCMV infection is due, in part, to the induction of the immunosuppressive molecules PD-L1 and IL-10 by type I IFNs. Although the exact molecular pathways by which type I IFNs modulate the expression of these immunesuppressive molecules are unknown, the above findings establish that, although type I IFNs mediate resistance to LCMV early during infection, they impair viral clearance during chronic infection.

In addition to viral strains and the stages of infection, mouse strains dictate the role of type I IFNs in LCMV infection. Although New Zealand Black mice clear the Armstrong infection efficiently, they succumb rapidly to Clone 13 challenge (185). Vascular leakage, inflammatory cell infiltration, and endothelial cell loss all contribute to the death of animals. The heightened susceptibility to Clone 13 infection is dependent on type I IFN signaling because cytokine receptor blockade prevents mortality of the infected mice (185). Interestingly, IFN-α concentrations are comparable in bronchoalveolar lavage fluid of Armstrong- and Clone 13–infected mice, suggesting that the elevated type I IFN signaling, rather than production, underlies the lethal type I IFN–mediated immunopathology in this model. It would be interesting to reevaluate the role of type I IFNs in viral infection using other mouse strains, because there clearly are differences among different laboratory strains.

HIV

HIV infection can lead to AIDS as the result of destruction of $CD4^+$ T cells (186). Type I IFNs are induced during HIV infection, predominantly by plasmacytoid dendritic cells (187). Although type I IFNs are known to mediate antiviral immunity, there has always been caution toward a detrimental role of type I IFNs during HIV/AIDS because of their proinflammatory nature (reviewed in Refs. 188, 189). Indeed, HIV disease progression is associated with increased IFN-α expression (190), and one clinical trial indicates that treatment with anti–IFN-α–neutralizing Abs delays disease progression (191).

Sustained type I IFN stimulation can negatively affect T cell function and survival. High levels of IFN-α inhibit T cell proliferation, as well as chemokine release, in vitro (192). Furthermore, type I IFNs promote apoptosis of $CD4^+$ T cells by inducing TRAIL (193), and patients with progressive HIV disease have higher expression levels of TRAIL and type I IFNs in lymphoid tissue (194). In addition to this proapoptotic pathway, type I IFNs were found to increase the expression of the proapoptotic protein Bak in $CD4^+$ and $CD8^+$ T cells, and T lymphocytes from HIV^+ patients express significantly higher levels of Bak than do those from HIV^- individuals (195). Importantly, small interfering RNA-mediated knockdown of Bak inhibited CD95/Fas-mediated death of T cells, suggesting that targeting this pathway could provide a novel therapy for limiting $CD4^+$ T cell loss in HIV-infected individuals. Therefore, type I IFN signaling is associated with increased T cell apoptosis and disease progression in HIV infection.

In addition, persistent type I IFN exposure can modulate IFN signaling in HIV. Although rhesus macaques treated with type I IFNs are more resistant to SIV infection, chronic type I IFN stimulation during infection renders cells refractory to further type I IFN stimulation by inducing negative regulators of type I IFN signaling, which leads to increased virus loads in treated animals compared with placebo controls (196). In a murine model of lymphopenia, chronic type I IFN exposure leads to $CD4^+$ T cell depletion and $CD8^+$ T cell expansion (197). Therefore, these findings suggest that type I IFNs promote $CD4^+$ T cell depletion independently of the effects of HIV and explain how neutralizing IFN-α may delay AIDS disease progression (191). Together, these data suggest that, although type I IFNs produced during the early phases of HIV infection are protective, persistent type I IFN signaling during chronic HIV infection is detrimental to the eradication of the virus and survival of the host cells.

Role of type I IFNs in bacterial and viral coinfection

Epidemiological studies indicate that concurrent infection by bacteria, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *S. aureus*, contributes significantly to the mortality caused by influenza A virus (IAV) infection (198). Protection against the extracellular bacteria requires efficient recruitment of neutrophils and macrophages to the site of infection (199, 200). Recent research established a role for type I IFNs in interfering with this innate defense mechanism.

In experimental models of IAV/bacterial coinfection, in contrast to WT mice, which succumb to secondary bacterial infection rapidly, *Ifnar1*$^{-/-}$ mice are highly resistant to secondary bacterial pneumonia (201). The enhanced bacterial clearance in *Ifnar1*$^{-/-}$ mice is due to increased neutrophil influx resulting from the upregulation of chemokines KC and Mip2, as well as elevated production of IL-17 (202, 203). *S. pneumoniae*–superinfected *Ifnar1*$^{-/-}$ mice show increased IL-17A production by pulmonary γδ T cells (203). IL-17 is a potent regulator of neutrophil recruitment through induction of KC, Mip2, and other inflammatory mediators (204). In addition to their major inhibitory role in neutrophil recruitment, production of type I IFNs during IAV and *S. pneumoniae* coinfection was reported to suppress macrophage influx due to downregulation of *Ccl2* (205).

In addition to extracellular bacteria, type I IFNs may play a role in regulating host resistance to superinfection with intracellular bacteria. IAV and mycobacteria coinfection leads to reduced Ag-specific T cell responses associated with decreased MHC class II expression on dendritic cells (206). Moreover, IAV was shown to impair control of *M. tuberculosis* in a type I IFN–dependent manner (207). The mechanisms underlying the regulatory function of type I IFNs in superinfection with intracellular bacteria remain to be elucidated.

Conclusions

Although type I IFNs are essential for defense against viral infections, they are now shown to impair resistance to a diverse range of pathogens. The beneficial or detrimental function of these cytokines in an infection is complex and is likely to be dependent on the type of host response triggered, as well as the combinations of host and pathogen factors, such as mouse background and pathogen species. For example, although, in many infections reviewed in this article, the main detrimental function for type I IFNs is to interfere with IFN-γ–dependent pathogen clearance programs, this clearly is not the only mechanism by which the cytokines impair host immunity. In addition, because type I IFNs can be produced by, and signal in, hematopoietic and nonhematopoietic cells, their functions in vivo also will be determined by the tissue sites and stages of infection. Although the effects of type I IFNs on immune cell functions have been the focus of recent studies (summarized in Fig. 1), the role of the cytokines in regulating the response of nonhematopoietic cells to infection should be examined carefully in future investigations. Identification of the pathways mediating the inhibitory function of type I IFNs will lead to a better understanding of the mechanisms underlying persistent infection and assist in developing novel therapeutics.

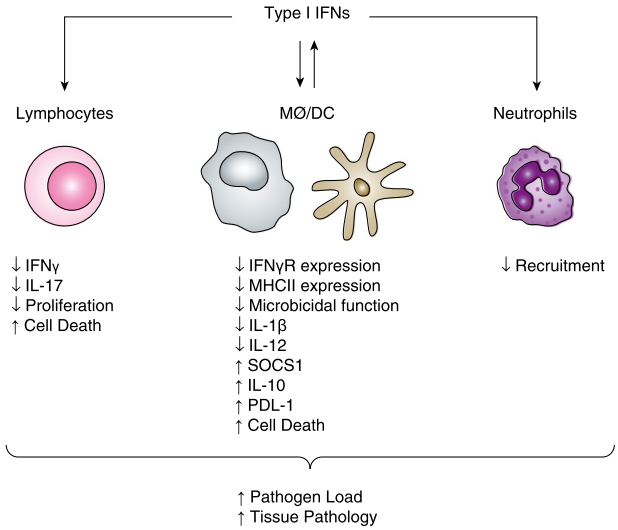

FIGURE 1. Type I IFNs modulate immune cell functions to impair host resistance to infection. Type I IFNs suppress cytokine production and survival of lymphocytes. Type I IFN signaling in macrophages and dendritic cells inhibits IFN-γ–dependent MHC class II expression and intracellular pathogen killing. Type I IFNs also promote the expression of immunosuppressive molecules (SOCS1, PDL-1, and IL-10) and the death of macrophages. In addition, type I IFNs prevent neutrophils from migrating into the site of infection, thereby contributing to increased susceptibility to bacterial pathogens following viral infection.

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Disclosures

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